2012

Is Etanercept A Safe and Effective Treatment For Ankylosing Spondylitis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2011

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not etanercept is a safe and effective treatment for ankylosing spondylitis (AS).

Study Design: Review of three English language randomized control trials published in 2007, 2008, and 2010.

Data Sources: Two double-blind placebo-controlled randomized controlled trials and one placebo-controlled randomized control trial comparing etanercept to placebo were found using PubMed.

Outcomes Measured: Work instability was measured through the Ankylosing Spondylitis Work Instability Scale (AS-WIS) based on scores of 1-20. Quality of life was measured through the EuroQOL-5D (EQ-5D), which assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Physical functioning was evaluated through the Bath Ankylosing Spondylitis Functioning Index (BASFI) where scores for functional limitation range from 1-100. Lastly, the safety and tolerability of etanercept were assessed based on personal reports from the patients themselves.

Results: In a study by Barkham et al, etanercept treatment was not found improve work instabililty but not to the point of statistical significance. Risk of job loss was also decreased in those who received etanercept treatment. Quality of life was considerably improved with etanercept therapy as seen in a RCT by Braun et al. This study also illustrated statistically significant improvement in physical functioning in those who obtained etanercept verse placebo. Long-term treatment with etanercept for 192 weeks was shown to be safe and tolerable in a study conducted by Davis et al. The most common adverse effect of etanercept therapy was injection site reaction where more reactions were present compared with placebo.

Conclusions: The results of two of the randomized control trials demonstrate etanercept to be a safe and effective treatment for ankylosing spondylitis. One randomized control trial does not reach statistical significance.

Key Words: Ankylosing Spondylitis, Etanercept

INTRODUCTION

Ankylosing spondylitis (AS), one of the spondyloarthropathies, is a type of inflammatory arthritis that has an effect on the axial skeleton, and if severe, other parts of the body. Inflammation of the spinal joints can cause chronic pain and possible spinal immobility due to fusing of vertebrae over time.[1] Ankylosing spondylitis affects men two to three times more than women and greatly impacts one's quality of life. There is no current cure for AS; however, many drugs and therapies have been studied for symptom reduction, pain control and improvement of quality of life.[2] This paper assesses three randomized control trials evaluating the effectiveness and safety of etanercept (Enbrel®) as a treatment for AS.

Although AS only affects 0.25% of the population, it is of importance to Physician Assistant practice due to the impact the disease can have on a person's life. Low back pain is one of the most frequent reason for a visit to a primary care physician, and 5% of those presenting with this pain have a spondyloarthropathy present.[3] Low back pain is often the presenting complaint of those with AS. Another frequent finding among those with AS is the gene protein Human Leukocyte Antigen (HLA)-B27 which is seen in 7% of the US population. This gene protein is present in 90% of persons with AS.[2] Knowledge of this frequent finding allows the Physician Assistant to be able to help reduce the patient's chronic pain and systemic effects, slow down eventual immobility, and improve quality of life. An average of $6,720 is spent on each of the estimated 30,000 AS patients who visit their primary physicians each year.[4,5]

The precise cause of AS is unknown, but genetics are thought to play a role with the gene protein HLA-B27. Ankylosing spondylitis can be present without HLA-B27 due to a possible immune-mediated reaction pathogenesis, because environmental factors or bacterial infections

(especially gastrointestinal) can prompt AS in those inclined. Tumor necrosis factor (TNF)-α, T_H17 T cells, CD4+ and CD8+ T cells, macrophages, and abundant transforming growth factor (TGF)-β are all thought to play a role in this immune-mediated reaction.[2] Ankylosing spondylitis usually presents around 20-30 years of age and begins with complaints of low back pain. Acute painful flare-ups and remissions characterize AS, and involvement of bilateral sacroiliac joints is a hallmark feature.[6] A diagnosis of AS is based on many factors since there is no specific diagnostic criteria for it. The patient may have pain upon palpation of the spine and sacroiliac joints and a positive Schober test: stretching of the skin upon spinal flexion of less than 15 cm between the sacral dimples and 10 cm above that.[6] Anterior uveitis is the most common extra-articular manifestation of AS affecting 1/3 of the patients at least once.[1] Other manifestations of AS are peripheral arthritis, enthesitis around the pelvis and calcaneus, inflammatory bowel disease, and decreased chest expansion.[6]

Treatment for AS should always begin with non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs have been shown to improve range of motion and decrease pain, allowing for better daily functioning.[2] All patients with AS should be involved in a physical therapy exercise program to help maintain posture and further improve mobility. Anti-TNF α therapy such as infliximab, adalimumab, and golimumab has shown to have a positive impact on symptom reduction and slowing disease progression and is another form of treatment commonly used. Surgery is a last resort treatment for those not responding to any other form of therapy. Common surgeries performed are total hip arthroplasties and spinal osteotomy with fixation.[6]

Symptom control has been the main aim for treatment through NSAIDs and exercise. Etanercept (Enbrel), an anti-TNF α drug commonly used for treatment of rheumatoid arthritis, has been revealed to both rapidly suppress disease activity and decrease symptoms in those with

AS.[7,8] Improving symptoms when other treatment options have failed can greatly increase one's quality of life.

OBJECTIVE

The objective of this systematic review is to determine whether or not etanercept is a safe and effective treatment for ankylosing spondylitis. Previous randomized control trials have determined etanercept as both a safe and effective treatment for ankylosing spondylitis.

METHODS

Specific selection criteria of three randomized control trials (RCT) were used for this review. One of these RCTs was an open label extension (OLE). The population chosen was patients (both men and women) $\geq$ 18 years of age with ankylosing spondylitis. The interventions utilized in each RCT were either etanercept 25mg subcutaneously twice per week[7,9] or etanercept 50mg subcutaneously once per week[8]. Comparisons were made between 25mg or 50mg etanercept to a placebo. Outcomes measured in each study were all based on patients oriented evidence that matters (POEMs). One outcome is change in work instability which is defined as "a state in which the consequences of a mismatch between an individual's functional abilities and the demands of his or her job can threaten continuing employment if not resolved".[7] Quality of life including physical functioning, vitality, social functioning, mental health, physical and emotional role limitations, bodily pain, general health, and fatigue was also assessed.[8] Lastly, safety associated with adverse events and tolerability of etanercept were measured.[9]

Key words used in the searches were "etanercept" and "ankylosing spondylitis". All articles search were published in peer-reviewed journals and in the English language. The author researched the studies through PubMed and selected the articles based on POEMs. Inclusion criteria consisted of studies that were randomized control trials published after 1996 with

participants over the age of 18 years old. Exclusion criteria included articles with disease-oriented evidence (DOE), published before 1996, or with participants under the age of 18 years old. The statistics used in the studies were 95% confidence intervals (CI), ANCOVA, ANOVA, Fisher's exact test, and χ^2 analyses all converted into p-values.

OUTCOMES MEASURED

Outcomes measured were based on scales or actual patient reports. Work instability was measured through the Ankylosing Spondylitis Work Instability Scale (AS-WIS), which measures the risk of job loss on a scale of 1-20. Low risk scores are those <11, medium risk ranges from 11-18, and high risk is 19-20.[7] Quality of life was assessed by the EuroQOL-5D (EQ-5D) which includes five aspects of health such as mobility, self care, usual activities, pain/discomfort, and anxiety/depression.[8] Included in quality of life is vitality, social functioning, mental health, physical and emotional role limitations, bodily pain, general health, and fatigue. The Bath Ankylosing Spondylitis Functional Index (BASFI) was used to measure physical functioning based on 10 different daily functioning questions each with a Likert scale ranging from 1 (easy) - 10 (impossible) on each question. The highest score possible is 100, which means the physical functioning is severely impacted. Some questions included are "Bending from the waist to puck up a pen from the floor without aid" and "standing unsupported for 10 minutes without discomfort".[10] Safety and tolerability of etanercept were both measured based on actual reports of patients participating in the study.

RESULTS

The three randomized control trials in this systematic review compared etanercept to placebo. Two of the studies were 12-week experimentations (Barkham, Braun) and one was 192

weeks (Davis). Patients in each study were allowed to continue on a steady dose of disease-modifying antirheumatic drugs (DMARDs) and NSAIDs. DMARDs permitted in all three were

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Barkham, 2010[4]	RCT	40	Placebo mean- 39.4; Etanercept mean- 40.8	Patients currently working with active AS, but were unstable at work with an AS-WIS >10	Past or current tuberculosis, congestive heart disease, or treatment in the preceding month with glucocorticoids	0	Randomized to receive 25mg etanercept or placebo subcutaneously 2x/week for 12 weeks
Braun, 2007[5]	RCT	361	18-70	Patients with active AS and morning stiffness $\geq$30 according to the visual analog scale along with 2 of the following: VAS for assessment of disease activity or nocturnal and total pain $\geq$30; BASFI $\geq$30	Patients previously exposed to TNF-α inhibitors	5	Randomized to receive 50mg etancercept 1x/week or placebo
Davis, 2008[6]	RCT (OLE)	277	Mean- 41.6	Patients with active AS previously enrolled in a RCT, who chose to continue on with an open-label extension	Patients previously treated with an anti-TNF besides etanercept	131	Randomized to receive 25mg etanercept subcutaneously 2x/week for the first 72 weeks, then 50mg etanercept in two doses of 25mg subcutaneously 1x/week or placebo

methotrexate and sulfasalazine, while hydroxychloroquine was only allowed in Braun and Davis' experiments. Corticosteroids begun two weeks proceeding to enrollment were acceptable in both Braun and Davis' studies.

In the study by Barkham et al, all 40 participants remained throughout the 12 weeks. No statistical significance was found with overall AS-WIS scores (p=0.160); however, there was improvement of scores with a 95% CI with a mean decrease of 2.75 in the etanercept group compared to a decrease of 0.68 in placebo (table 2).[7] Table 3 shows risk of job loss, where there was a greater decrease in the risk of job loss for the etanercept group of 55% contrasted to the placebo group who had only 35% decrease.[7] The relative risk reduction (RRR) was calculated to be 57.1% and absolute risk reduction (ARR) was 20%. Numbers needed to treat (NNT) was calculated as 5, meaning 5 people need to be treated with etanercept in order to prevent one person from work instability with AS.

Table 2: Changes in AS-WIS scores in those who received etanercept verse placebo

Treatment Group	Mean AS-WIS decrease
Etanercept	-2.75
Placebo	-0.68

Table 3: Risk of job loss

CER	EER	RRR	ARR	NNT	p-value
35%	55%	57.1%	20%	5	0.160

The study conducted by Braun et al was based on modified intention to treat where the population includes patients who received at least one dose of etanercept or placebo. There were 356 participants who made up this population, and 321 completed the study (90%). At the

beginning of the study, a large number of patients reported issues in the 5 aspects of the EQ-5D scale: 79.8% reported problems with mobility, 89.9% with usual activities, 64.6% admitted to anxiety/depression, 57% had problems with self care, and 99.2 reported pain or discomfort. Statistically significant improvements ($p<0.01$) in all the EQ-5D categories were reported. After 12 weeks of treatment, 66% of etanercept patients had clinical benefit with improvement compared to 50% of those with placebo as shown in table 4.[8] The relative benefit increase (RBI) was calculated to be 32% and absolute benefit increase (ABI) was 16%. NNT was calculated as 2, meaning 2 people need to be treated with 50mg etanercept once a week for 12 weeks in order to improve 1 person's quality of life compared to control. Statistically significant improvements in the etanercept group were also seen with the BASFI from weeks 2-12 (table 5). At week 2, the BASFI score decreased by 15 ($p<0.05$), week 4 by about 22 ($p<0.001$), week 8 about 25 ($p<0.0001$), and by week 12 the score decreased by approximately 27 ($p<0.0001$). No statistically significant difference in the BASFI was seen with the placebo group: week 2 score decreased about 7 and weeks 4-12 had a decrease of roughly 10.[8]

Table 4: Benefit of etanercept on improvement in EQ-5D

CER	EER	RBI	ABI	NNT	p-value
50%	66%	32%	16%	2	P<0.01

Table 5: Improvement in BASFI scores in etanercept group compared to placebo

Group	Week 2	Week 4	Week 8	Week 12
Etanercept	-15 ($p<0.05$)	-22 ($p<0.001$)	-25 ($p<0.0001$)	-27 ($p<0.0001$)
Placebo	-7	-10	-10	-10

The study by Davis et al was an open label extension (OLE) of 168 weeks from a 24-week experiment. There were 277 participants in the original study and 257 continued with the OLE. Of these 257 participants, 129 received placebo and 128 received 50mg etanercept once a week. Only 126 of these patients went on to complete the entire course of the experiment, accounting for a 49% loss. The majority of losses were due to patient refusal, followed by adverse effects, lack of efficacy, lost to follow-up, protocol violation, protocol requirement, and lastly physician decision. Etanercept 50mg once per week was given to everyone for the 168 weeks of the OLE. Treatment with etanercept over 192 weeks was overall found to be safe. Results were compared to the placebo group from the original RCT (table 6). The most common adverse event was injection site reactions (ISR), and from the original 257 enrolled in the OLE, 57 (22.2%) reported an ISR. Of the 139 who received placebo in the RCT, 13 (9.4%) reported an ISR.[9] The relative risk increase (RRI) calculated was 139% and absolute risk increase (ARI) was 12.8%. Numbers needed to harm (NNH) was 8 meaning for every 8 people treated with etanercept for 192 weeks, 1 person will be harmed with an ISR compared to control. Table 7 shows other adverse events of long-term etanercept treatment. Serious adverse events were only reported from 33 participants (12.8%) with depression being the most common (1.2%). Infections were also common in those treated with etanercept and developed in 187 (72.8%) participants compared to 43 (30.9%) with placebo. The most common infections were upper respiratory infections (45%) and sinusitis (16%). No deaths were reported from this study.[9]

Table 6: Harms from injection site reactions of those treated with 192 weeks etanercept compared to 24 weeks placebo

CER	EER	RRI	ARI	NNH
9.4%	22.2%	139%	12.8%	8

Table 7: Adverse events of long-term etanercept treatment compared to placebo

	ISR	Infections	Serious Adverse Events	Depression	Death
Etanercept	57 (22.2%)	187 (72.8) URI: 45% Sinusitis: 16%	33 (12.8%)	3 (1.2%)	0
Placebo	13 (9.4%)	43 (30.9%)	4 (2.9%)	Not Reported	0

DISCUSSION

This systematic review investigated the three RCTs for the safety and effectiveness of etanercept as a treatment for AS. The studies by Braun et al and Davis et al demonstrated this drug as a safe and effective treatment. Statistical significance was not reached in the study conducted by Barkham et al; however, a relatively beneficial NNT of 5 still allows for some efficacy.

Ankylosing spondylitis is a progressive disease with no current cure that can eventually develop into immobility, so treatment to improve the lives of these patients is important. Etanercept has been established to be a safe way to improve the quality of life and daily functioning of those with AS. This drug has also been FDA approved for the treatment of moderate to severe rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and moderate to severe chronic plaque psoriasis.[11] Although etanercept is an expensive drug, insurance companies work with the patient to cover most if not all of the cost. There is currently no generic available in the U.S. An ENBREL *support*™ Card is also available to provide assistance for eligible patients in need.[11,12] Contraindications to treatment include a previous hypersensitivity reaction to the drug or any part of its formulation and any individual with sepsis.

It is also important not to administer live vaccines while undergoing treatment.[11] Boxed warnings for infections and malignancy are currently in place due to adverse events that have been seen in those using etanercept. Severe infections including tuberculosis, invasive fungal, bacterial, viral, and opportunistic infections have been noted, and lymphoma and other malignancies have been seen in children.[11]

There were various limitations among the studies presented in this review. A small sample size of 40 participants in the Barkham et al study may not have been sufficient enough for a proper representation of the AS population. The Davis et al study was carried out for an exceedingly long period of time, which may be a major contribution to the 51% participant loss by the end of the 192 weeks. For all three studies, results may have been impacted by a variation in occupations, daily activities, and lifestyles of each participant.

CONCLUSION

Etanercept is a safe treatment for AS and effective for improving quality of life and physical functioning as revealed by this review. Effectiveness for work instability was seen, but not enough to prove statistical significance. Future studies on work instability should be performed with participants who have the same or similar occupation. Another direction for future research should be aimed at a way to reduce adverse events associated with etanercept treatment. Anti-TNF α therapy is becoming more widely used among the AS population. It would be beneficial so determine the differences in outcomes between etanercept and other commonly used Anti-TNF α drugs such as infliximab, adalimumab, and golimumab. Continuing research on treatment for AS should provide those with the disease an opportunity to live a less painful and debilitating life.

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